Remarks

Claims 1, 4-11, 13, 17, 28, 36-41, 46, and 49-65 are pending in the application, with claim 1 being the independent claim. Claims 2 and 3 are sought to be canceled without prejudice or disclaimer. Amendments are requested to claims 1, 4, 5, and 10. Support for the amendment to claim 1 may be found in claims 2 and 3 as filed. The remaining amendments merely adjust dependencies to account for the cancellation of claims 2 and 3. No new matter is believed to have been added by these amendments, and their entry is respectfully requested. Claims 5-7, 9, 13, 17, 28, 36-39, 41, 46, 53, 56, 58, and 60-65 stand withdrawn as being drawn to various non-elected species. Upon a finding of allowable generic subject matter, Applicants maintain their request for rejoinder and examination of the withdrawn claims.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Rejections under 35 U.S.C. § 103(a)

1. First 35 U.S.C. § 103(a) Rejection

Claims 3, 4, 10, 11, 49-51, 54, 55, 57, and 59 are rejected under 35 U.S.C. § 103(a), as allegedly being obvious over Donda *et al.* (*Canc. Immun. 3*:11 (2003)) ("Donda") in view of U.S. Publ. No. 2002/0071842 A1 ("the '842 publication"), Fujii *et al.* (*Nat. Immunol. 3*:867-875 (2002)) ("Fujii"), PCT Publ. No. WO 99/64597 A1 ("the '597 publication"), and an alleged admission made in the specification. Claim 3 has been canceled, rendering the rejection of this claim moot. Insofar as the rejection applies to

the remaining claims, including claim 1 into which certain limitations of claim 3 have been incorporated, Applicants respectfully traverse this rejection.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103(a) based upon the clear factual findings. The factors to be considered under 35 U.S.C. § 103(a), are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 383 U.S. 1, 17 (1966); MPEP § 2141, and *KSR Int'l Co v. Teleflex Inc.*, 550 U.S. 398, 415 (2007).

The Office has recently published updated Examination Guidelines to aid Examiners in formulating obviousness rejections. *See Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex* Fed. Reg. Vol. 75, pp. 53643 to 53660 (September 1, 2010), hereinafter "the guidelines." The guidelines helpfully walk through a variety of different rationales in which obviousness may or may not be established, based on recent Federal Circuit case law. The guidelines discuss some general categories of rationales available to Examiners in making rejections under 35 U.S.C. §103, including combining known elements with predictable results, substituting one known element for another with predictable results, or an "obvious to try" rationale where only a finite number of predictable solutions existed to a well-recognized problem. In all cases the Examiner must demonstrate a link between the rationale and a legal conclusion through explicit factual findings (see, *e.g.*, the guidelines at 53644, col. 3), and the Examiner must consider all rebuttal evidence presented by the Applicant (see, *e.g.*, the guidelines at 53657, col. 1).

In attempting to arrive at the claimed invention, the Examiner has reached into the cited references to find elements to combine, elements to substitute for other elements, and indeed has sampled from a decidedly non-finite repertoire of possible combinations or substitutions to arrive at the claimed compound. As explained in detail below, Applicants respectfully submit that the Examiner has failed to demonstrate that a person of ordinary skill in the art would have had sufficient reason to combine and/or substitute the various elements chosen by the Examiner from the cited references to predictably arrive at the claimed compound, in view of the myriad other directions the cited references more reasonably point. In addition, the Examiner has failed to demonstrate that the person of ordinary skill in the art would have had any expectation that the claimed compound would work for its intended purpose.

In support of the arguments presented in this Reply, Applicants refer to the attached Declaration of Ernest S. Smith Under 37 C.F.R. § 1.132 ("the Smith Declaration"). In his Declaration, Dr. Smith provides a detailed factual analysis of the references cited by the Examiner, and his expert assessment of what the references would have provided to a person of ordinary skill in the art. The Examiner is respectfully reminded that the Smith Declaration properly presents factual evidence rebutting the Examiner's alleged *prima facie* case of obviousness, and as such must be considered on the record. *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007).

In order to understand the Examiner's rationale in making the obviousness rejection above, it is instructive to summarize the structure and intended purpose of the present invention. The compound of the invention was devised to activate certain powerful, yet non-specific elements of the ***innate immune system*** (CD1d-restricted NKT

cells), and to specifically recruit those elements to act at a precise target of interest, such as a tumor cell. Smith Declaration at paragraph 4. To achieve these goals the inventors created a compound comprising a functional, antigen-loaded CD1d molecule attached to a binding molecule which specifically binds to a cell-surface marker. *Id.* The compound functions without requiring a subject to mount any sort of acquired or adaptive immunity to a specific antigen.

In constructing the obviousness rejection Examiner has used the claimed invention as a template with which to select various elements of Donda, the '842 publication, Fujii, and the '597 publication, thereby concluding that a person of ordinary skill in the art would have allegedly been motivated to start with the composition described in Donda, directed to stimulating acquired or adaptive immunity, and to then choose, combine, and substitute elements from the '842 publication, Fujii, and the '597 publication as the Examiner has done in order to produce the claimed compound

> in order to protect against targeted tumors by activation of NKT cells, particularly in light of the teaching of Fujii *et al* that α-GalCer binds to and is presented by CD1d to NKT cells that are useful in controlling resistance to tumors, and in light of the disclosure of US 2002/0071842 A1 that an CD1d-IgG fusion protein comprising α-GalCer is useful to enhance or induce protective immunity to cancer.

(Office Action at page 5.)

Applicants respectfully disagree. Applicants submit that one of ordinary skill in the art would not have seen a reason to modify the composition described in Donda in the way the Examiner has done, and indeed would have had strong motivation to go in an entirely different direction, because the composition described in Donda, even in view of the myriad additions and substitutions which might be selected from the supporting references, was clearly created with the objective of improving the stimulation of

acquired or adaptive immunity through the recruitment of antigen-specific, MHC-restricted CD8 T cells. The Donda publication demonstrates successful achievement of the objective in a specialized model system, and suggests ways to expand upon the results, by further exploiting adaptive immunity. Accordingly, the skilled person would had no reason to totally abandon the successful teachings of Donda to go in the entirely different direction of employing non-specific innate immunity provided by CD1d-restricted NKT cells.

Indeed, as explained by Dr. Smith, in order to arrive at the claimed compound the Examiner has misinterpreted certain of the supporting references. When interpreted properly, the very references cited by the Examiner underscore the clearly-recognized unpredictability in the art of immunotherapy modalities at the time the application was filed.

The Donda publication aims to exploit the power of CD8 T cells to target tumor cells. As explained in paragraphs 8 and 9 of the Smith Declaration, Donda utilized a highly specialized mouse model to show that a specific MHC molecule combined with a specific peptide can be fused to a TAA-specific antibody to recruit MHC/antigen-specific CD8 T cells to the site of the tumor, thereby promoting CTL-mediated cell lysis. *Id.* at paragraph 8. The result was demonstrated by insuring that the vast majority of CD8+ T cells in the experimental mice were H-2K^b/ova peptide-specific (*Id.*), thereby sidestepping the normal extensive polymorphism of MHC class I molecules, and the normal small subset of H-2K^b/ova peptide-specific CD8 T cells that would be available for recruitment. Smith Declaration at paragraph 9.

As Dr. Smith points out, however, Donda emphasized the criticality of using MHC-restricted, antigen-specific CD8 T cells to achieve the result of killing tumor cells. *Id.* at paragraph 9. Accordingly, Donda suggested using MHC/peptide combinations which would be known to specifically activate highly abundant T-memory cells, *e.g.*, by using peptides from common viruses. *Id.* Dr. Smith notes that Donda believed that this adaptation of the disclosed system would exploit "the strongest immune defences of our organism." *Id.* Finally, Dr. Smith notes that nothing in Donda "even hints at the prospect of going in the completely different direction of eliciting a non-specific ***innate immune response***." *Id.*

As pointed out in the guidelines, "[a] claimed compound would not have been obvious where there was no reason to modify the closest prior art lead compound to obtain the claimed compound and the prior art taught that modifying the lead compound would destroy its advantageous property." Guidelines at p. 53651, col. 1, *citing Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.* 533 F.3d 1553 (Fed. Cir. 2008). Donda stresses that the "advantageous property" of the MHC class I/peptide/antibody complexes described in the invention is the powerful cytotoxic potential of MHC-restricted, antigen-specific CD8 T cells. By substituting a non-MHC molecule (CD1d) which recruits non-antigen-specific NKT cells which function in an entirely different way from CD8 T cells, the modification proposed by the Examiner (*e.g.*, substituting the MHC class I molecule of Donda with the CD1 molecule described in the '842 publication in view of the knowledge that α-GalCer-pulsed dendritic cells can stimulate NKT cells as taught by Fujii) would destroy the advantageous property (targeting the cytotoxic properties of

CD8 T cells to tumor cells) of the composition described by Donda. Simply put, the person of skill in the art would have no reason to make the modification.

Indeed, Donda cautions against straying too far from the disclosed technology by noting that tumor immunotherapy strategies are highly unpredictable. Smith Declaration at paragraph 11. As Dr. Smith notes, given the unpredictability described by Donda, "the skilled scientist, encouraged by Donda's results . . ., would have been motivated to continue along the same lines using compositions which lead to improved stimulation of antigen-specific CTLs of the adaptive immune system." *Id.*

On these facts alone, the person of ordinary skill in the art would have had no reason to substitute the successful elements of the composition described in Donda with technologies described in the '842 publication, Fujii, or the '597 publication, because making the substitutions constructed by the Examiner would have destroyed the advantageous properties of the composition described in Donda. Thus, under the Federal Circuit's holding in *Eisai*, and further in view of the clear unpredictability of tumor immunotherapies, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 4, 10, 11, 49-51, 54, 55, 57, and 59 under 35 U.S.C. § 103(a).

Even if the skilled person were to, by chance, combine the references cited by the Examiner, that person would not predictably arrive at the claimed invention. In particular, Dr. Smith points out that the Examiner has misinterpreted the teachings of the '842 application, which is largely directed to a screening method and which *at most* briefly describe an immunotherapy method which again utilizes ***acquired or adaptive immunity***. As Dr. Smith explains, the '842 application is directed to a screening method

to utilize a CD1 molecule fused to a non-antigen-specific IgG Fc portion to identify CD1 ligands of an immunogen (*e.g.*, a bacteria, virus, allergen, or tumor), which might subsequently be used to elicit an adaptive immunogen-specific CD1-restricted T-cell response to other antigenic components of the immunogen. Smith Declaration at paragraph 12. The '842 neither teaches nor would lead the skilled person to combine the screening molecule of the reference with a TAA-targeting antibody. Insofar as the Examiner asserts that the '842 publication discloses that "a CD1d-IgG fusion protein comprising α-GalCer is useful to enhance or induce protective immunity to cancer," Dr. Smith explains that, again, the aim is to stimulate or enhance acquired or adaptive immunity to cancer-associated antigens. Smith Declaration at paragraph 14. In this context, the '842 publication teaches administration of a CD1-IgG Fc fusion protein with a specific and separate immunogen that contains a CD1d ligand "in order to enhance acquired or adaptive immunity to that immunogen. . ." *Id.* Thus, not only would the skilled person, in reading Donda have no reason to stray from the use of MHC class I molecules to elicit antigen-specific MHC-restricted CTLs into the world of innate immunity, were the skilled person reading Donda to, by chance, combine it with the '842 publication, that person would *still* have no reason to look to innate immunity.

Given that no reason would exist to modify either Donda or Donda combined with the '842 publication to substitute the elicitation of innate immunity rather than adaptive immunity, the skilled person would have no reason to look up references such as Fujii. Even if, by chance, Fujii was reviewed by the skilled person to introduce the concept of innate immunity, Dr. Smith points out that "Fujii does not provide any evidence of predictability regarding anti-tumor immunotherapy modalities comprising

cell-free CD1d molecules..." Smith Declaration at paragraph 15. Instead, according to Dr. Smith, "Fujii suggests that presenting α-GalCer as a complex with CD1d on dendritic cells is more effective to recruit and activate CD1d-restricted NKT cells than presenting the same α-GalCer on other CD1d-expressing cells." *Id.* The skilled person reading Fujii would reasonably conclude that soluble CD1d, or even CD1d expressed on non-dentritic cells "would not be effective to recruit, activate and maintain CD1d-restricted NKT cells." *Id.* The statements in Fujii thus *clearly teach away* from claimed compositions.

Finally, as noted by Dr. Smith, the '597 publication merely discusses methods for generating MHC class I fusion proteins, a compound that would be utilized to elicit or enhance an acquired, or adaptive T cell response. Smith Declaration at paragraph 16. Thus the '597 publication does not provide any facts that would make the compounds of the present invention, which exploit innate immunity, any more predictable.

In sum, the person of ordinary skill in the art, starting with the composition of Donda, would simply have no reason to substitute or add elements from the '842 publication, Fujii, or the '597 publication. Furthermore, even if by chance the skilled person were to make the combinations and substitutions constructed by the Examiner, the skilled person would not predictably arrive at the compounds claimed in the present invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 4, 10, 11, 49-51, 54, 55, 57, and 59 under 35 U.S.C. § 103(a).

2. Second 35 U.S.C. § 103(a) Rejection

Claims 1-4, 8, 10, 11, 40, 49-52, 54, 55, 57, and 59 have been rejected under 35 U.S.C. § 103(a), as allegedly being obvious over U.S. Publ. No. 2003/0166277 A1 ("the '277 publication") in view of the '842 publication, Fujii, the '597 publication, and an alleged admission made in the specification. Claims 2 and 3 have been canceled, rendering the rejection of these claims moot. Insofar as the rejection applies to the remaining claims, Applicants respectfully traverse this rejection.

Similar to Donda, the '277 publication discusses using anti-tumor antibodies to target one or more MHC/peptide complexes to tumor cells, thereby recruiting and stimulating CD8 T cells. In constructing the second obviousness rejection, the Examiner has again used the claimed invention as a template with which to select various elements of the '277 publication, the '842 publication, Fujii, and the '597 publication, and to conclude that a person of ordinary skill in the art would have been motivated to start with the composition described in the '277 publication, directed to stimulating acquired or adaptive immunity, and to then choose, combine, and substitute elements from the '842 publication, Fujii, and the '597 publication as the Examiner has done in order to produce the claimed compound. Office Action at page 7.

Applicants respectfully disagree. As with Donda, Applicants submit that one of ordinary skill in the art would not have seen a reason to modify the composition described in the '277 publication in the way the Examiner has done, and indeed would have had strong motivation to go in an entirely different direction, because the composition described in the '277 publication, even in view of the myriad additions and substitutions which might be selected from the supporting references, was clearly created

with the objective of improving the stimulation of acquired or adaptive immunity through the recruitment of antigen-specific, MHC-restricted CD8 T cells. Accordingly, the skilled person would had no reason to totally abandon the teachings of the '277 publication to go in the entirely different direction of employing non-specific innate immunity provided by CD1d-restricted NKT cells.

According to Dr. Smith, the '277 publciation emphasizes "the need to identify and utilize improved antigenic peptides to improve stimulation of antigen-specific, MHC-restricted T cells . . .," again to further exploit and improve acquired or adaptive immunity. Smith Declaration at paragraph 18. Thus, the '277 publication recommends using MHC-restricted peptides from common pathogens, to induce high frequencies of CTLs that are specific for the peptide:MHC complex, and to use these to "redirect" antigen-specific CTLs to tumors. *Id.* Furthermore, as with Donda, nothing in the '277 publication suggests going in the completely different direction of eliciting a non-specific ***innate immune response.***

As with Donda, the '277 publication stresses that the "advantageous property" of the MHC class I/peptide/antibody complexes described in the invention is the powerful cytotoxic potential of MHC-restricted, antigen-specific CD8 T cells. By substituting a non-MHC molecule (CD1d) which recruits non-antigen-specific NKT cells which function in an entirely different way from CD8 T cells, the modification proposed by the Examiner (*e.g.*, substitute the MHC class I molecule of Donda with the CD1 molecule described in the '842 publication in view of the knowledge that α-GalCer-pulsed dendritic cells can stimulate NKT cells as taught by Fujii) would destroy the advantageous property (targeting the cytotoxic properties of CD8 T cells to tumor cells)

of the composition described in the '277 publication. Simply put, the person of skill in the art would have no reason to make the modification.

On these facts alone, the person of ordinary skill in the art would have had no reason to substitute the successful elements of the composition described in the '277 publication with technologies described in the '842 publication, Fujii, or the '597 publication, because making the substitutions constructed by the Examiner would have destroyed the advantageous properties of the composition described in the '277 publication. Thus, under the Federal Circuit's holding in *Eisai*, and further in view of the clear unpredictability of tumor immunotherapies, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1, 4, 8, 10, 11, 40, 49-52, 54, 55, 57, and 59 under 35 U.S.C. § 103(a).

The '842 publication, Fujii, the '597 publication are analyzed above in the first 103 rejection, and the facts presented relating to combining these documents with Donda apply similarly to their use in combination with the '277 publication. In sum, the person of ordinary skill in the art, starting with the composition of '277 publication, would simply have no reason to substitute or add elements from the '842 publication, Fujii, or the '597 publication. Furthermore, even if by chance the skilled person were to make the combinations and substitutions constructed by the Examiner, the skilled person would not predictably arrive at the compounds claimed in the present invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1, 4, 8, 10, 11, 40, 49-52, 54, 55, 57, and 59 under 35 U.S.C. § 103(a).

II. Obvious-Type Double-Patenting Rejections

Claims 3, 4, 8, 10, 11, 40, 49, 50, 51, 54, 55, 57, and 59 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claim 78 of co-pending U.S. Appl. No. 12/034,737 in view of Pavlinkova *et al., Cancer Immunology and Immunotherapy 49*:267-275 (2000) ("Pavlinkova"), U.S. Publ. No. 2002/0071842 A1, Donda, PCT Publ. No. WO 99/64597 A1, and an alleged admission in the specification. Applicants respectfully traverse this rejection.

Claims 1-4, 8, 10, 11, 40, 49, 50, 51, 54, 55, 57, and 59 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claim 78 of co-pending U.S. Appl. No. 12/034,737, Pavlinkova, U.S. Publ. No. 2002/0071842 A1, Donda, PCT Publ. No. WO 99/64597 A1, and an alleged admission in the specification. Applicants also respectfully traverse this rejection.

The present application claims the benefit of the September 27, 2002 priority date. Co-pending U.S. Appl. No. 12/034,737 was filed on February 21, 2008. Even assuming, *arguendo*, that the present application is afforded the benefit of only the corresponding PCT filing date of September 26, 2003, the present application is still the earlier-filed application.

Further, Applicants wish to direct the Examiner's attention to M.P.E.P. § 804, which recites:

> If a "provisional" nonstatutory obviousness-type double-patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Claim 78 in co-pending U.S. Appl. No. 12/034,737 is drawn to a non-elected invention and, therefore, has not yet been examined. Applicants believe that the claims of the present application are now in condition for allowance, with the ODP rejections as the last remaining rejections. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw these rejections.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 2116
ROBERT *et al.*	Art Unit: 1644
Appl. No.: 10/529,221	Examiner: DIBRINO, Marianne N.
Filed: June 30, 2006	Atty. Docket: 1843.0200001/EJH/M-N
For: **Targeted CD1d Molecules**	

Declaration of Ernest S. Smith Under 37 C.F.R. § 1.132

Mail Stop AF

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, Ernest S. Smith, declare and state that:

1. I received my Ph.D. in Microbiology and Immunology from the University of Rochester School of Medicine. A copy of my *curriculum vitae* is attached hereto as Exhibit A.

2. I am currently employed as the Senior Vice President of Research and the Chief Scientific Officer of Vaccinex, Inc. I am experienced in molecular and cellular immunology.

3. I have read and understand the above-identified application, the pending claims, as well as the Office Action of July 8, 2010.

4. I understand that the pending claims are directed generally to a compound comprising a CD1d complex and an antibody specific for a cell-surface marker, where the CD1d complex comprises a CD1d molecule loaded with an alpha-galactosylceramide antigen, and where the CD1d molecule is linked to the antibody. Essentially, the antibody portion of the claimed compound targets the CD1d complex to a cell or tissue

expressing the cell-surface marker. The antigen-loaded CD1d molecule acts by recruiting CD1d-restricted NKT cells to the cell or tissue expressing the cell-surface marker, and activating the NKT cells to produce large amounts of IFN-γ and IL-4. Thus, the claimed invention has the following special features: (i) the monomorphic nature of the alpha-galactosylceramide-loaded CD1d molecule, which can activate a broad spectrum of CD1d-restricted NKT cells, and (ii) the ability to specifically recruit and activate CD1d-restricted NKT cells to tissue or cells expressing the cell-surface marker, thereby facilitating and localizing an ***innate immune response***. *See, e.g.,* paragraphs [0023] and [0197] of the specification.

5. I have been advised by Vaccinex's Patent Counsel that the pending claims stand rejected as allegedly being obvious over Donda *et al., Cancer Immunity 3*:11 (2003) ("Donda") in view of US Publ. No. 2002/0071842 A1, Fujii *et al., Nature Immunology 3*:867-875 (2002) ("Fujii"), PCT Publ. No. WO 99/64597 A1 and an alleged admission in the specification in the sequence listing for SEQ ID NO: 40.

6. I have further been advised that the Examiner is arguing that a skilled scientist would have been motivated, upon reading the cited references, to generate the claimed CD1d complex to treat a cancer patient (e.g., with a tumor expressing the surface antigen Her2/neu) through the recruitment and activation of CD1d-restricted NKT cells.

7. I disagree. Upon reviewing the documents relied upon by the Examiner, it is my opinion that a skilled scientist would not have been motivated to generate the claimed CD1d complexes, and furthermore would not have had a reasonable expectation that the claimed complexes would successfully facilitate the destruction of targeted

tumors for the following reasons. First, a skilled scientist would have sought methods to improve the recruitment of antigen-specific CTLs rather than to look to NKT cells. In other words, the skilled scientist would not have seen a reason to modify compounds used to elicit an ***adaptive immune response*** to yield the claimed compounds which elicit an ***innate immune response***. Second, the cited documents indicate that there was considerable unpredictability at the time even as to whether those compounds that utilize the adaptive immune response to target tumor-associated antigen would be effective *in vivo*, outside of highly specialized model systems. These reasons are discussed in greater detail below.

8. Donda, the first reference the Examiner relies upon, aims to sensitize tumor cells to CD8 T-lymphocytes by exposing tumor cells to an antibody specific for a tumor-associated antigen ("TAA"), where the antibody has been chemically conjugated or fused to a specific MHC molecule loaded with a specific peptide antigen. Donda's very specialized model system makes use of the OT-1 mouse line which overproduces CTL with a T-cell receptor specific for the immunodominant peptide of ovalbumin (amino acids 257-264) recognized in the context of the MHC class I H-2K^b. The antibody portion of Donda's compounds targets CEA-expressing tumor cells while the MHC/peptide portion recruits and activates the abundant H-2K^b/ova peptide-specific CD8 T-lymphocytes to the tumor cell location, thereby facilitating tumor cell lysis. *See* page 2 of Donda. In this model, more than 90% of the CD3-positive cells express the transgenic ovalbumin peptide: H-2K^b-specific T-cell receptor. *See* p. 6. In the first experiment the OT-1 mice were grafted with CEA-expressing tumor cells and were then treated with the antibody-MHC/peptide conjugate. Tumor growth was delayed relative

to non-treated control mice. In a second model system, CEA-expressing transgenic mice were given $5x10^7$ OT-1 splenocytes by adoptive transfer. These transferred H-$2K^b$/ova peptide-specific T cells were then activated by immunization with OVA, which resulted in 12-40% of CD8+ cells in these mice being H-$2K^b$/ova peptide-specific. *See* p. 8. Tumor grafts were introduced into the mice, which were then treated with the antibody-MHC/peptide conjugate. Again, tumor growth was delayed relative to non-treated controls. *See* p. 8 and Fig. 6.

9. Donda's highly specialized experimental design sidestepped at least two problems that might be encountered in using antibody/MHC/peptide complexes to target CTLs to tumor cells, *i.e.*, the extensive polymorphism of classical MHC class I molecules and the small subset of CTL/peptide-specific CD8 T-lymphocytes that would normally be available for recruitment to the tumor location. Donda et al. clearly recognized the limitations of their model system, and suggested that the way to overcome the limitations would be to use

> various TAA mAbs conjugated to autologous MHC containing well-defined antigenic viral peptides derived from common viruses such as influenza, EBV, or CMV, against which they have an active T-cell memory that could eventually be boosted by viral vaccination.

See p. 12. The authors suggest that the system needs an even more robust use of the ***adaptive immune system***, noting that "human beings have learned to develop high-affinity T cell clones [to common viral antigens], probably representing the strongest immune defences of our organism." *See* p. 12. Nothing in the article even hints at the prospect of going in the completely different direction of eliciting a non-specific ***innate immune response***.

10. In contrast, the presently claimed invention goes in an entirely different, non-antigen-specific direction, making use of the monomorphic CD1d complex loaded with α-GalCer which is suitable for the activation of CD1d-restricted NKT cells possessing an invariant receptor, an arm of the innate immune system, in a peptide antigen-independent manner.

11. The Examiner asserts that Donda does not "teach wherein the compound used for targeting and tumor cell destruction comprises a CD1d complex rather than an MHC complex, nor wherein the antigen bound to the CD1d molecules is α-GalCer, nor the linker that is SEQ ID NO: 2." *See* page 4 of the Office Action. I concur. Instead of leading the skilled scientist in the direction of CD1d-restricted NKT cells for an ***innate immune response***, Donda, as explained above, informs the skilled scientist of ways to enhance the recruitment of peptide-specific CD8 T lymphocytes for an ***adaptive immune response***. Indeed, Donda indicates that there was unpredictability in the art with respect to other *in vivo* tumor immunotherapy strategies. For example, Donda discusses

> [t]he use of bispecific antibody with one arm directed against a TAA and the other against a T cell receptor-associated protein, such as CD3, or an NK cell activating receptor, such as CD16, was proposed eighteen years ago with elegant *in vitro* results. However this strategy has not led to convincing *in vivo* therapy results on solid tumors, most likely due to a lack of T cell activation by the bispecific antibodies.

See p. 10 (internal citations omitted). Thus, the predictability of successfully treating a solid tumor *in vivo* in a clinical setting would have been low in general, and thus the skilled scientist, encouraged by Donda's results in their highly specialized model system, would have been motivated to continue along the same lines using compositions which lead to improved stimulation of antigen-specific CTLs of the adaptive immune system.

12. I have been advised that the Examiner relies on the combination of Donda and U.S. Publ. No. 2002/0071842 A1 to assert that the claimed invention is obvious. I submit, however, that the Examiner has incorrectly interpreted the functions of the compounds and the components disclosed in U.S. Publ. No. 2002/0071842 A1, which, like Donda, is aimed at eliciting acquired or adaptive immunity against a component of a disease causing agent such as a CD1d ligand containing bacteria, virus, allergen or tumor. The cited reference discloses a CD1d-IgG Fc fusion protein and methods for using the same to ***identify*** CD1 ligands of an immunogen and eliciting ***immunogen-specific*** CD1-restricted T cells. *See, e.g.,* paragraph [0004] and [0038] of the reference. The fusion proteins disclosed in U.S. Publ. No. 2002/0071842 A1 lack the antigen-binding domains of an antibody (*e.g.,* heavy and light chain variable regions). In fact, the reference clearly and repeatedly references IgG2a fragments having only a hinge region and CH2 and CH3 domains. *See* paragraphs [0166]-[0167] of the cited reference. Accordingly, it is not the antibody fragment portion of the fusion protein that is used to recognize antigens (*e.g.,* TAA on tumor cells), but the CD1 portion of the fusion protein that is used to identify new CD1 ligands which are recognized by CD1-restricted T cells. Accordingly, the only "antigen" associated with the fusion protein of the cited reference is a CD1 ligand associated with the disease causing agent (bacteria, virus, allergen or tumor). The following table depicts the compounds discussed thus far in terms of their respective components and activities:

	Donda	**U.S. Publ. No. 2002/0071842 A1**	**Claimed Invention**
Targeting Component	CEA-specific monoclonal antibody	None	Antigen-specific antibody
"Effector"	H-2K^b/ova peptide	CD1-Fc fusion protein	galactosylceramide-

component			loaded CD1d complex
Exemplary Use	Recruitment of H-2K^b/ova peptide-specific CTLs to kill CEA-expressing tumor cells	Identification of CD1 antigens and CD1-restricted T cells	Recruitment of CD1d-restricted NKT cells to express large amounts of IFN-γ and IL-4 to induce a cascade of immune effectors at the tumor site
Immune Response	Adaptive Immunity	None when employed to screen CD1d ligands and CD1d-restricted NKT cells or Adaptive Immunity to disease causing agents that comprise a CD1d ligand	Innate Immunity

13. I submit that the skilled scientist would lack the requisite motivation to combine Donda and U.S. Publ. No. 2002/0071842 A1, to predictably arrive at the claimed invention based on the collection of individual compound components as disclosed in each of these references, especially since the CD1d complex of U.S. Publ. No. 2002/0071842 A1 is primarily used as a screening tool rather than a therapy.

14. The Examiner asserts that U.S. Publ. No. 2002/0071842 A1 provides disclosure that "an CD1d-IgG fusion protein comprising α-GalCer is useful to enhance or induce protective immunity to cancer." While this may be the case in one aspect of the invention (see, e.g., paragraphs [0030]-[0033]), the cited reference is referring to CD1-IgG Fc fragment administered in combination with a specific (and separate) immunogen that contains a CD1d ligand in order to enhance ***acquired or adaptive*** immunity to that immunogen. The "protective immunity" to cancer results from immunization of the subject with a specific immunogen (eliciting an adaptive immune response), and only indirectly from the administration of the CD1-IgG Fc fusion protein. Similarly, the "therapeutic application" suggested in Example 5 is directed to acquired or adaptive

immunity to specific CD1 antigens identified as components of a disease causing agent according to the methods of the reference. As with Donda, nothing in the reference would lead the skilled scientist to turn to the utilization of molecules and cells for mobilization of the innate immune system with CD1d ligands that are unrelated to a targeted antigen or immunogen. Rather the skilled scientist reading the reference in combination with Donda would seek to find new CD1 ligands that comprise a disease causing agent as specific immunogenic targets for CD1-restricted T cells.

15. Accordingly, neither Donda nor U.S. Publ. No. 2002/0071842 A1 would provide any reason for the skilled scientist to explore references related to innate immunity, such as Fujii. The skilled scientist reading Donda and/or U.S. Publ. No. 2002/0071842 A1 would instead be looking to find improved ways to stimulate aquired or adaptive immunity. Fujii discusses the (unrelated) ability of α-GalCer-pulsed dendritic cells to stimulate NKT cells triggering the release of large amounts of cytokines. Furthermore, Fujii does not provide any evidence of predictability regarding anti-tumor immunotherapy modalities comprising cell-free CD1d molecules or any suggestion which would lead the skilled scientist to generate the claimed ***targeting*** compounds. Indeed, Fujii suggests that presenting α-GalCer as a complex with CD1d on dendritic cells is more effective to recruit and activate CD1d-restricted NKT cells than presenting the same α-GalCer on other CD1d-expressing cells. It would, therefore, be reasonably concluded from Fujii that soluble complexes of CD1d or CD1d targeted to other types of cells than dendritic cells or expressed on dendritic cells in a context

different from integral membrane CD1d would not be effective to recruit, activate and maintain CD1d-restricted NKT cells.

16. PCT Publ. No. WO 99/64597 A1 discusses various methods for generating MHC class I fusion proteins. The PCT reference does not provide evidence of predictability in the art of immunotherapy modalities or anything that would lead a skilled scientist in the direction of generating the claimed ***targeting*** compounds which elicit an ***innate immune response***.

17. It is also my understanding that the pending claims have been rejected in the Office Action as allegedly being obvious over U.S. Publ. No. 2003/0166277 A1 in view of U.S. Publ. No. 2002/0071842 A1, Fujii, PCT Publ. No. WO 99/64597 A1, and an alleged admission made in the specification.

18. Much the same as Donda, U.S. Publ. No. 2003/0166277 A1 discusses coupling anti-tumor antibodies to one or more ***MHC/peptide*** antigen complexes, with the aim of stimulating peptide-antigen-specific T cells through ***adaptive immunity***. Indeed, U.S. Publ. No. 2003/0166277 A1 emphasizes the need to identify and utilize improved antigenic peptides to improve the stimulation of antigen-specific, MHC-restricted T cells. *See e.g.*, paragraphs [0055]-[0071]. As with Donda, the aim of U.S. Publ. No. 2003/0166277 A1 is to redirect the highly potent adaptive immune reactions to

> target an otherwise evasive tumor. The immune response to commonly encountered pathogens (e.g., influenza virus) and/or pathogens against which individuals are likely to have been vaccinated (e.g., influenza, or tetanus) is associated with induction of a high frequency of high avidity T cells that are specific for immunodominant peptide:MHC complexes infected with these pathogens. These same . . . T cells can be redirected to tumors by linking the dominant peptide:MHC ligands recognized by these t cells to a tumor-specific antibody specificity."

See paragraph [0101]. As with Donda, the skilled scientist will be motivated to find better immunospecific peptide antigens. Thus, for the same reasons discussed above with respect to Donda, the combination of references relied upon by the Examiner in this second rejection would not lead the skilled scientist in the direction of successfully or predictably producing the claimed invention which exploits ***innate immunity***.

19. I further declare that the above statements made of my own knowledge are true and the above statements based on information and belief obtained from the references and documents discussed are believed to be true. Additionally, I declare that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Title 18 United States Code Section 1001, and that willful false statements may jeopardize the validity of this application or any patent issuing thereon.

20. I have read, I am familiar with, and I understand, the provisions of 37 C.F.R.§§ 11.18(b) and (c) relating to the effect of signature and certificate for correspondence filed in the U.S. Patent and Trademark Office.

Date: November 17, 2010

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EDUCATION

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1992 – 1994	Laboratory Assistant, St. John Fisher College, Rochester, NY
1994 - 1998	Pre-doctoral Fellow, University of Rochester, Rochester, NY
1998 – 2001	Director, Molecular Immunology, Vaccinex Inc., Rochester, NY
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2003 – 2008	Chief Scientific Officer, Vice President, Research, Vaccinex Inc., Rochester, NY
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Honors and Awards

1992	Delta Epsilon Sigma National Scholastic Honor Society
1993	St. John Fisher College Award for Excellence in the Natural Sciences
1995-1998	Awarded Pre-doctoral Fellowship, Immunology USPHS Training Grant

Publications

Merchlinksy, M., D. Eckert, **E. Smith**, and M. Zauderer. 1997. Construction and Characterization of Vaccinia Direct Ligation Vectors. *Virology* **238**: 444-451.

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Alan Jonason, Terrence L. Fisher Sebold Torno, Holm Bussler, Ji Li, Laurie Winter, Renee Kirk, Alan Howell, Jeff Caplan, Patrick Kenney, Christine Reilly, Maria Scrivens, Elizabeth E. Evans, Mark Paris, Raymond Watkins, Maurice Zauderer, John E. Leonard, **Ernest S. Smith.** Antibody Mediated Neutralization of Sema4D Reduces Tumor Angiogenesis and Growth *In Vivo*. Presented at AACR April 2010 Washington, DC.

E. Smith, T. Fisher, C. Reilly, J. Li, L. Winter, A. Jonason, J. Seils, R. Kirk, C. Cornelius, T. Richards, J. Caplan, P. Kenney, L. Croy, J. Veeraraghavan, T. Pandina, S. Torno, E. Evans, M. Paris, J. Leonard, R. Watkins, M. Zauderer. Development of anti-SEMA4D monoclonal antibody for the treatment of multiple sclerosis. Presented at ECTRIMS. Gothenburg, Sweden October 2010

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Smith, E.S., et al 2001. Lethality Based Selection of Recombinant Genes in Mammalian Cells: Application to Identifying Tumor Antigens. Oral Presentation. Presented at the Regional Cancer Center Consortium for Biological Therapy of Cancer, Pittsburgh, PA.

Smith, Ernest S. Attenuation of experimental autoimmune encephalomyelitis by treatment with anti-CD100 Monoclonal Antibodies. Presented at Semaphorin Function & Mechanisms of Action. Paris 2008

Ernest S. Smith, Leslie Croy, Wei Wang, Maria Scrivens, Tracy Pandina, Christine Reilly, Ekaterina Klimatcheva, Terry Fisher, Holm Bussler, Sumedha Bhagat, Mark Paris and Maurice Zauderer. Antibody Selection from Immunoglobulin Gene Libraries Expressed in Mammalian Cells. PEGS Recombinant Antibody Conference. Boston May 2010

Ernest S. Smith Antibody Selection from Immunoglobulin Gene Libraries Expressed in Mammalian Cells. Presented at "Designing Efficacious, Potent and Tailored Antibody Therapeutics For Increased Clinical Efficacy and Utility. Boston, MA October 2010.

Issued Patents

Methods of Directly Selecting Cells Expressing Inserts of Interest
Inventors: Maurice Zauderer and **Ernest S. Smith**
US Patent 7,067,251
Issued June 27, 2006

In vitro Methods of Producing and Identifying Immunoglobulin Molecules in Eukaryotic Cells
Inventors: Maurice Zauderer and **Ernest S. Smith**
European patent: EP1340088B1
Issued January 17, 2007

Selection Of Human TNF alpha Specific Antibodies
Inventors: **Ernest S. Smith,** Leslie A. Croy, Maria G.M. Scrivens
US Patent 7,807,168
Issued October 5, 2010

GRANT REVIEWER

Member NCI Immunology Special Study Section. March 2006, June 2008 and June 2010

Teaching Experience and Other Invited Presentations

Lecturer, Chemical Engineering 469 University of Rochester 2006, 2007, 2008, 2009

St. John Fisher College School of Pharmacy. All Sciences Seminar Series: "Introduction to Therapeutic Monoclonal Antibodies. September 2007.

SUNY Brockport Chemistry Department Seminar: "Introduction to Therapeutic Monoclonal Antibodies. September 2008.

Cornell University: "Introduction to Therapeutic Monoclonal Antibodies. March 2009.

University of Rochester: Biomedical Engineering and Industry in New York. Introduction to Vaccinex. March 2009

GRANT SUPPORT

SBIR 1R43AR048072-01 08/01 – 07/02 $100,000 NIH NIA
GENETIC SELECTION TO CLONE CHONDROGENIC REGULATORS
The objective of this work was to develop a functional gene selection platform using a proprietary vaccinia virus library technology.

SBIR 1R43CA108032-01 04/04 – 03/06 $610,000 NIH NCI
NEW TARGET ANTIGENS FOR PROSTATE CANCER IMMUNOTHERAPY
The objective of this study was to validate 14 differentially expressed prostate tumor antigens discovered by peptide elution from prostate tumor and normal cells from the same cancer patient.

SBIR 5 R43 AI056624-02 04/04 – 03/06 $1,366,185 NIH NIAID
HUMAN MONOCLONAL ANTIBODIES FOR BIOTERRORISM DEFENSE
The objective of this work was to identify and functionally validate fully human monoclonal antibodies that can neutralize vaccinia virus and smallpox infection.

ATP Award #70NANB4H3002 05/04-04/06 $2,000,000 NIST ATP
DEVELOPMENT OF A HUMAN MONOCLONAL ANTIBODY DISCOVERY TECHNOLOGY
The primary objectives of this study were to 1) select fully human monoclonal antibodies specific for C35, a Vaccinex breast cancer antigen and 2) to develop antibody selection technology to allow for the screening of antibody libraries against antigens expressed by whole cells.